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Investigating cell migration inducing and hyaluronan binding protein in central nervous system development and disease

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Abstract

Myelin ensheaths axons and increases their conduction velocities. In the central nervous system (CNS) myelin is produced by oligodendrocytes (OLs) that differentiate from oligodendrocyte progenitor cells (OPCs) throughout life. Demyelination and neurodegeneration are observed in many forms of white matter injury and disease, one of which is multiple sclerosis (MS). OPCs accumulate and fail to differentiate into OLs within MS lesions, inside which there is an increase in the levels of extracellular hyaluronic acid (HA), a linear glycosaminoglycan polymer that can be mega-Daltons in size. HA fragments produced by the enzymatic digestion of high molecular weight HA have been shown to inhibit OPC differentiation and myelin formation. There is debate as to which specific hyaluronidase generates these smaller, inhibitory HA fragments. One promising candidate, CEMIP (cell migration inducing and hyaluronan binding protein), is expressed by OPCs and has increased expression levels in MS and an MS animal model called experimental autoimmune encephalomyelitis (EAE). Increased CEMIP expression leads to the breakdown of extracellular HA; this activity is blocked by a selective hyaluronidase inhibitor that was also shown to promote OPC maturation and remyelination in an animal model of white matter injury. Furthermore, increased CEMIP expression inhibits the differentiation of OPCs to OLs in vitro. Future studies will investigate if the HA fragments produced by CEMIP inhibit OPC differentiation and myelin formation, as well as if inhibition of CEMIP activity induces remyelination in white matter lesions and EAE. These studies could lead to the identification of CEMIP as a new therapeutic target to promote functional remyelination in a variety of demyelinated lesions, such as preterm white matter injury and MS.